CAFFEINE TO SUSTAIN OPERATIONAL FATIGUE

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Sleep deprivation and desynchronization from circadian rhythm are common in military operation. Caffeine is the most widely used psychostimulant and may be useful in operational fatigue-coping strategies. In this paper we will review the current policies on caffeine in the military, then we will discuss effects and potential use of a slow release caffeine formulation.

1. Current caffeine use in the military.

1.1. Pharmacology.

Caffeine is a naturally occurring xanthine derivative (table I). Metabolism is virtually confined to the liver. Caffeine half life is prolonged in pregnancy and with oral contraceptives, and is shortened in smokers and heavy caffeine users. Its stimulant effect is connected to the blocking of A_1 adenosine receptors. Caffeinism syndrome is observed with too much caffeine consumption. Symptoms are : restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal (GI) complaints, muscle twitching, palpitation, psychomotor agitation. Caffeine withdrawal may cause headache, fatigue, anxiety, insomnia, nausea, performance impairments. Symptoms are observed between 12 hours and 1 week after the last caffeine intake, with a peak intensity at 48 hours.

Table I: Caffeine dietary sources	
coffee	60-120 mg/cup
Tea	40-60 mg/cup
Hot chocolate	20 mg/cup
Soft drinks	40 mg/360 ml serving
Chocolate bar	20 mg/bar

1.2. Caffeine in the USAF.

In the USAF in 1995 (1), caffeine was recommended as a stimulant for enhancing vigilance, alertness, mood or to delay sleep. Flight surgeons had to be aware of its diuretic effect that may increase dehydration on prolonged flights. Caffeine intake was to be avoided within 6 hours of bed time and the tablet form was not authorized.

1.3. Caffeine in the US Navy.

A survey conducted aboard USS America during Desert Shield and Desert Storm operations over Iraq showed different patterns of caffeine use. In the attack community A-6 aviators used to drink 2 cups per day, whereas F-14 aircrew drunk 3-4 cups per day. Most caffeine was ingested on non flying days during Desert Shield and on days with flight during Desert Storm. Shorter nap duration was associated with greater caffeine use (2).

Another survey was done on USS Independence in 1992 during Operation Southern Watch over Iraq (3). It provided data about the most commonly used performance maintenance modalities in aircrew during 18 days of intensive carrier operation (table II). Coffee and caffeine tablets were the most consumed stimulants.

Currently in the US Navy, caffeine is the only approved chemical for use to promote alertness in prolonged operations. No limits on caffeine intake are set, but aircrew are grounded if they present any side effects.

Table II: commonly use performance maintenance modalities (US Navy, Belland & Bissel,1994).	
modality	*number*
none	44
coffee	39, average 1-2 cups before flying
caffeine tablets (75 mg)	18
no response	05
candy	05
soda	04
snuff tobacco	03
iced tea	03
nicotine gum	02
tobacco cigarettes	02

1.4. Caffeine in the French military.

Coffee is not restricted for French aircrew, and caffeine tablets are not approved.

2. Slow Release Caffeine (SRC).

2.1. Pharmacokinetics.

This SRC formulation increases the mean delay to peak plasma concentration (C_{max}) and lowers the C_{max} (table III). We evaluated the effects of SRC in 2 sleep deprivation experiments.

Table III: caffeine/SRC pharmacokinetics				
Caffeine 300 mg/60kg	C_{max} µg/ml plasma	T_{max} h	$T_{½}$ h	AUC µg/ml plasma. h
Aqueous solution	6.9 ± 0.3	1.2 ± 0.2	5.4 ± 0.6	57.8 ± 4.9
Slow release	5.5 ± 0.3	4.1 ± 0.3	5.1 ± 0.6	54.2 ± 6.4

2.2. 34-hour sleep deprivation.

2.2.1. Protocol.

In this double blind, placebo (PBO) controlled, cross over study, we evaluated SRC 300 mg in 24 sleep deprived young healthy subjects (4). The 12 females (using oral contraceptives) and 12 males volunteers

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(mean age 24 years) came at the laboratory at 06:00h, on day 1 (D1) and were maintained awake until the end of the session on D2 at 17:30h. They took the treatment (PBO or SRC 300 mg) at time zero (H0), which took place between 00:00h and 01:30h. Alertness, mood, subjective sleep and performance were assessed during 2-hour session tests at H2, H9 and H13, with a 34 h maximum sleep deprivation. The tests included : blood pressure and heart rate monitoring, psychomotor tests, Standardized Test for Research with Environmental Stressors (STRES) battery (6), Multiple Sleep Latency Test (MSLT), focused attentional test (BATP), mood, alertness and sleep evaluation by visual analogue scales (VAS). Circulating caffeine levels were assessed in salivary samples.

2.2.2. Results.

With PBO, nausea and vomiting occured in 2 females volunteers. With SRC one male subjects complained of mild GI disorders and 4 female subjects reported mild tremor, nausea or palpitation.

Cardiovascular parameters were not influenced by treatment. Caffeine in women had a salivary peak concentration and bioavailability (AUC) higher than men : $C_{max\ salivary}$ = 4.7 µg/ml (female) versus 2.4 µg/ml (male), AUC = 77.6 µg/ml.h (female) versus 30.6 µg/ml.h (male). Caffeine half life (T ½) was longer in the female group : T ½ = 7.6 h (female) versus 4.8 h (male).

Sleep latency, evaluated by MSLT, was significantly longer with SRC (table IV). Most of performance improvements (STRES battery) occured at H9 for men and H9 and H13 for women. With PBO, female and male subjects reported similar scores for calmness and contentedness (Bond and Lader VAS) (5), whereas a decrease in alertness appeared in the female group. In both sexes, alertness was enhanced by SRC. During the recovery night, mean sleep duration, sleep onset latency and quality of sleep were not influenced by treatment.

Table IV: MSLT in minutes and seconds

Time H 0 = drug intake	PBO mean ± sem	SRC 300 mg mean ± sem
H 2.5	6:05 ± 1:50	11:40 ± 1:02
H 9.5	3:22 ± 0:45	4:40 ± 0:18
H 13.5	2:50 ± 0:49	4:30 ± 0.39

2.2.3. Discussion.

In this 34-hour sleep deprivation experiment, SRC action is extended in female subjects, who exhibited also more adverse events with both treatments, than their male colleagues. This sex effect may be explained by the higher sensitivity to sleep deprivation and higher circulating caffeine levels observed in female volunteers, who used oral contraceptives, known to prolong caffeine half life.

2.3. 64 hour-sleep deprivation.

2.3.1. Protocol.

In this double blind, placebo controlled, cross over study, 16 young healthy male volunteers were exposed to a 64 h sleep deprivation period, to evaluate the effects of SRC 300 mg (7). Subjects took SRC every 12 h, from D1 21:00h to D3 09:00h. Test sessions included: BATP and STRES battery and were performed 4 times per 24 h at 10:00h, 14:00h, 21:00h, 02:00h. During the recovery period (2 nights), sleep was limited to 8 h per night and subjects were tested only during the day: sessions R1 and R2 on D4 and R3 and R4 on D5.

2.3.2. Results.

Attentional performance (BATP) was better with caffeine than with PBO from 15 to 55 hours of sleep deprivation. Both treatments showed a sharp performance change after 41h (figure1). During

Figure 1: BATP, %

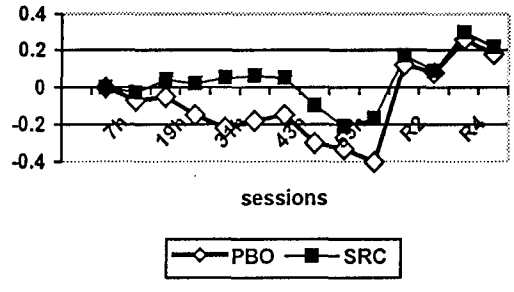


Figure 2: SPATIAL, error %

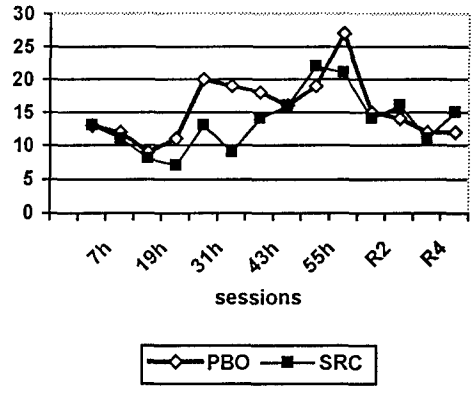
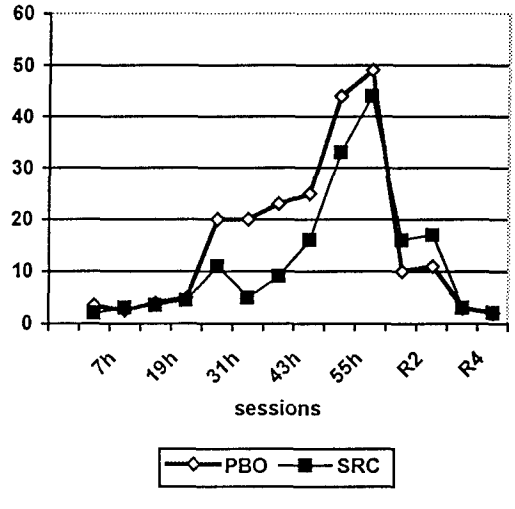


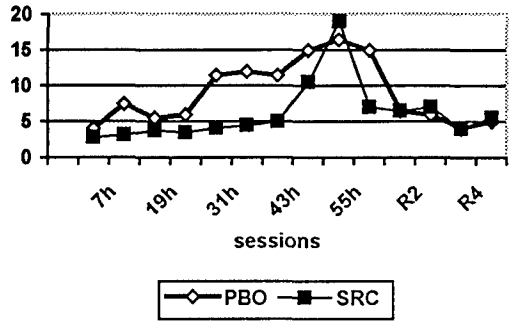
Figure 3: TRACKING, lost controls



recovery period, no difference was observed between treatment.

Performance of subjects was better with SRC whatever the STRES battery task (reaction time, mathematical, memory, spatial, tracking, dual tasks) up to 45 h of sleep deprivation (figures 2, 3, 4).

Figure 4: DOUBLE TASK memory/4 letters, error %



Conclusions.

Modern warfare exposes military personnel to sleep deprivation and desynchronization, while their tasks are more cognitively demanding. To maintain performance in such conditions, aircrew often rely on natural stimulants. Coffee is the most widely used and its acceptance, tolerance and side effects are well known. The development of a new slow-release caffeine formulation may optimize the caffeine consumption strategy in an operational environment. Due to its pharmacokinetic properties, SRC 300 mg is effective to maintain cognitive performance during limited (45 h) sleep deprivation. However, like an aqueous caffeine solution (coffee), SRC is not immune of adverse effects. Therefore SRC should be individually tested prior to operational use. Female subjects using oral contraceptives are more likely to express side effects.

Potential use also concerns desynchronization from physiological rhythm (jet-lag, night duty). A major experiment, Pegasus Operation, directed by Drs D. Lagarde and J. French, from IMASSA, Fr, and Brooks AFB, US, will address that issue. This study, completed in 1998, and involving 27 US military personnel flown from Texas to France, evaluated the use of SRC 300 mg, taken daily for 5 days, as a counter-measure to jet-lag.

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